PSJ17 Exh 109

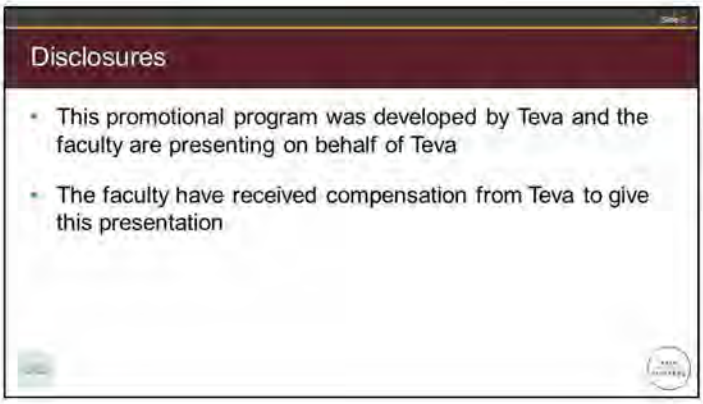
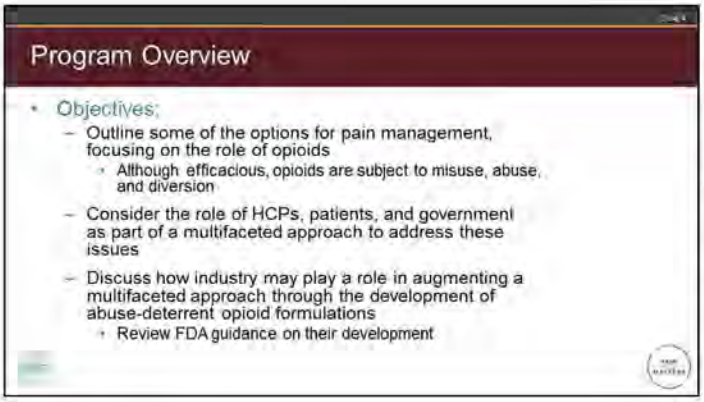
PAIN-40128 March 2015

Pain Matters: Evolving Roles, Same Goals Video Script/Storyboard

PARC Team:
Please note that the script was already reviewed and approved. All deviations from the previously approved script are also noted. In addition, please be advised that the video and slides have been uploaded as supporting documents.

Part 1 – Program Introduction and Overview

Slide #	Slide Image	Narration
		Introduction Music
1		**Gudin** Hello, my name is Dr. Jeff Gudin. I'm the director of pain management and palliative care at the Englewood Hospital and Medical Center in Englewood, New Jersey, and also a clinical instructor of anesthesiology at the Icahn School of Medicine at Mount Sinai. I want to welcome you to our program, entitled "Evolving Roles, Same Goals: The Changing Landscape of Pain Management."
2		**Gudin** Before we get started I'd like to take this opportunity to have our faculty introduce themselves. Dr. Argoff, why don't you start us off? **Argoff** I'm Charles Argoff, a professor of neurology at Albany Medical College and director of the Comprehensive Pain Center at Albany Medical Center in Albany, New York. **Gudin** Dr. Argoff will present "How A Multifaceted Approach Can Help Address Opioid Abuse."

		And Dr. Michael R. Brennan will discuss "Developing Abuse-Deterrent Opioids." Dr. Brennan? **Brennan** I'm Michael Brennan. I'm the medical director and chief medical officer of the Pain Center of Fairfield in Fairfield, Connecticut. I'm also associate medical director for the Chronic Pain and Recovery Center at the Silver Hill Hospital in New Canaan, Connecticut.
3		**Gudin** I also want to let you, our audience, know that this program was developed by Teva Pharmaceuticals, that the three of us are presenting on behalf of Teva, and that we've been compensated by Teva to give this presentation.
4		**Gudin** Over the course of this program, we will discuss some of the issues we all deal with on a day-to-day basis when managing pain. Specifically, we'll take a look at treatment options, focusing on opioids. As we all know, opioids are used to treat pain but abuse can occur. As such, it's important that we, as clinicians, understand when and how to use them. We will also examine a multifaceted approach to addressing issues associated with opioids, and how healthcare professionals, patients, and the government can also play a role.

		Finally, we'll take a look at how the development of abuse deterrent opioids may play a role in this multifaceted methodology, taking information from the ~~2013~~ 2015 FDA ~~Draft~~ Guidance on this topic.

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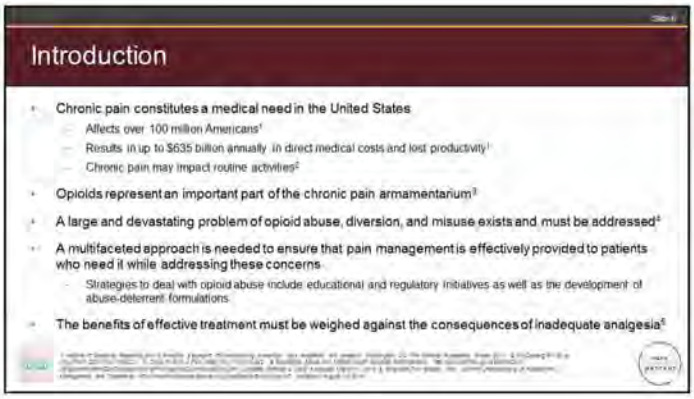
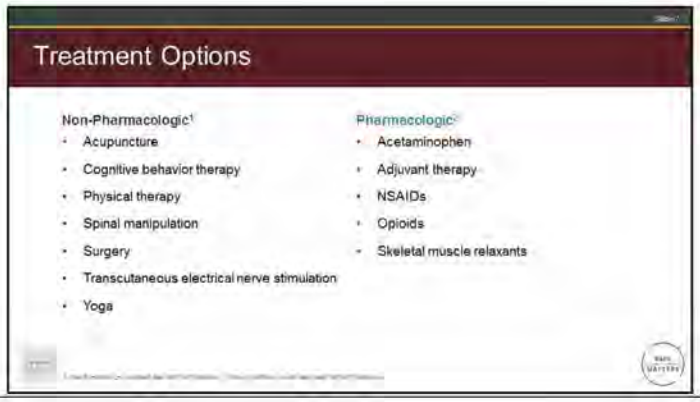
Part 2 – Complexities in Pain Management		
5		**Gudin** I would like to begin this program by talking about some of those day-to-day challenges a practitioner may face when it comes to pain management.
6		**Gudin** Chronic pain constitutes a significant medical need in the United States. We recognize that patients are living longer with chronic illnesses, surviving their trauma or cancer, and as a result, may also be experiencing chronic pain. We know that chronic pain affects over 100 million Americans and costs this country a significant amount of money, estimated at over 600 billion dollars annually in direct costs and lost productivity. And we know that there's a cost to patients as well, that chronic pain may impair routine activities.
7		**Gudin** Now, we know there are a few choices for analgesic medications, and opioid analgesics represent an important tool in our treatment arsenal. Unfortunately, with the expanding use of opioid analgesics, an epidemic of prescription opioid abuse has resulted.

		One of the challenges for those of us who treat pain patients has been how to utilize these important analgesics safely and effectively. And what we've recognized is that there's no simple solution. A multifaceted approach is needed to make sure that pain management is adequately provided to patients who need it, while we also deal with the issues such as abuse, misuse, and diversion of these substances. We have developed strategies to deal with opioid abuse, most notably focused around educating the many parties involved. The pharmaceutical industry has also stepped up and is trying to play a role in preventing the misuse and abuse of prescription analgesic medications. One way that they've done this is through the development of ~~abuse~~ abuse-deterrent formulations for opioids. And any time we treat pain patients, we as clinicians recognize the ~~the~~ balance in our treatments. So we have to provide patients with adequate analgesia, but minimize the adverse events associated with those medications, and not just the physiological adverse effects, but also the adverse effects of opioid abuse, misuse, and/or diversion.
8		**Gudin** I mentioned before that opioids are certainly an important

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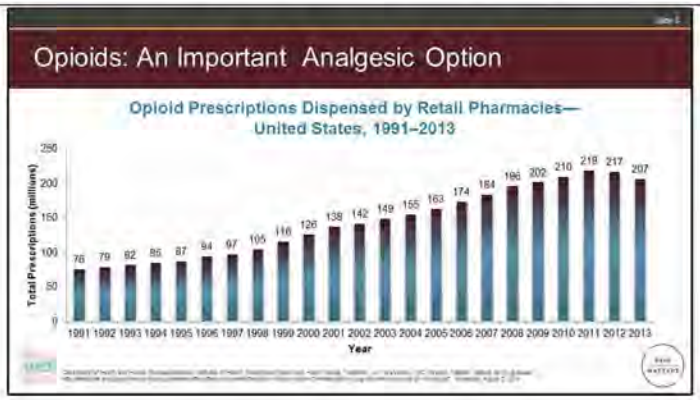
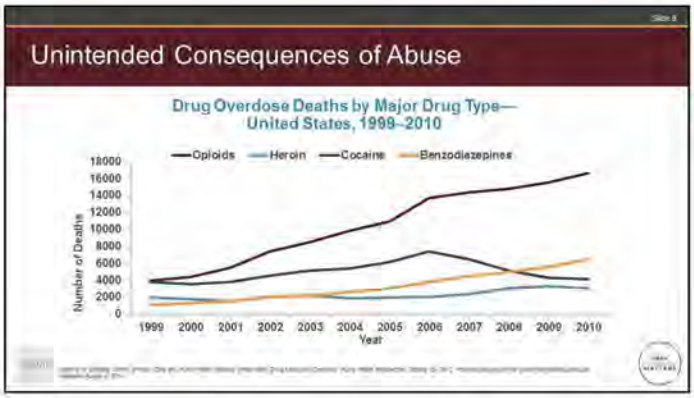
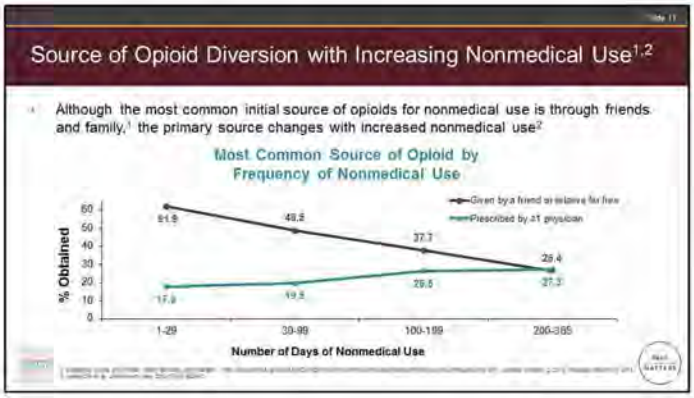
		analgesic option for pain management. This has been recognized over time. If you look at this chart, starting in the early 1990s, taking us up to 2013, you could see that there has been a slow, yet progressive increase in the amount of opioids dispensed by retail pharmacies in the United States. Again, this has to do with our improved abilities to assess pain and our willingness to treat chronic pain with a treatment regimen that includes opioids. Unfortunately, the greater volume of opioid analgesics has also resulted in issues related to misuse, abuse, and diversion of these important analgesics.
9		**Gudin** Beyond increased misuse and diversion, there has also been an increase in deaths due to drug overdose. As you can see in this chart, prescription opioids outrank both heroin and cocaine combined as a cause of drug overdose deaths here in the United States. Looking at the slope of these curves, you see that drug overdose deaths due to prescription opioid use has outpaced heroin and cocaine over the last 10 years or so, highlighting the need to develop strategies to prevent prescription opioid misuse and abuse.
10		**Gudin** David Fishbain, a psychiatrist and pain management specialist from the University of Miami,

		conducted an evidence-based review of the chronic pain literature, focusing on patients with non-cancer and non-malignant pain who were receiving chronic opioid analgesic therapy. He looked at 67 different studies that evaluated the abuse or addiction rate, aberrant drug-related behaviors, and urine toxicology testing. And what he found is that only 3.27 percent of patients being treated with chronic opioid therapy had a high likelihood of abuse or addiction with their opioid analgesics. Most notably, he found a 25 times lower rate of abuse or addiction in patients who didn't have a prior history of abuse or addiction. This is an important data set for us to recognize that the risk is clearly greater in patients with a previous history of abuse or addiction and that it's relatively low for patients with chronic non-malignant pain who don't have a previous history of addiction.
11		**Gudin** We all know that the most common initial source of opioids for non-medical use comes from a friend or family member for free, but as the frequency of non-medical use increases, the opioid becomes more likely to come from a clinician, highlighting the need for us to educate and reinforce to our patients how to use their medication appropriately.

		This brings us to the end of our discussion on some of the complexities clinicians face in pain management, and I hope you found this chapter informative. Please return to the main menu and select the next chapter to hear Dr. Argoff tell you more about the role that clinicians and others can play in addressing opioid abuse.
	Video Image	**Closing Music**

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Part 3 – Addressing Opioid Abuse: A Multi-Faceted Approach		
12		**Argoff** I'm Charles Argoff, professor of neurology at Albany Medical College and director of the Comprehensive Pain Center at Albany Medical Center in Albany, New York. In the previous chapter, you heard Dr. Jeff Gudin discuss some of the challenges we face with balancing the need for effective pain management with some of the dangers of prescription opioid use. To continue this conversation, I'll focus on how we can help address opioid abuse with a multifaceted approach.
13		**Argoff** There are many approaches to mitigate opioid abuse, and I would like to divide them into three main buckets. First, it's education that ensures clinicians understand how to screen, monitor, and manage patients appropriately with opioid therapy. This can also be combined with patient education on adherence to a treatment regimen, as well as appropriate storage and disposal of opioids. Second is the availability and use of tools that can help us guide the approach to managing a person on opioid therapy. For example, prescription drug monitoring programs, which have been

		developed in almost every state, help us as clinicians see what controlled substances our patients are currently being prescribed. We have also had scheduling changes regarding certain opioids. We have risk evaluation and mitigation strategies or REMS programs to help us guard against opioid abuse, changes to opioid labeling, and abuse-deterrent ~~draft~~ guidance from the FDA. The FDA ~~draft~~ guidance outlines how abuse deterrent properties can be tested and what claims the FDA might allow in the product's package insert based on study results.
14		**Argoff** It's important to recognize that there are multiple stakeholders who are involved in addressing opioid abuse and it is necessary for there to be a collaborative approach among these groups. These groups include healthcare professionals who are currently involved in managing patient care, the patients themselves, State and Federal government entities, as well as industry. To promote safe and effective pain management, we can incorporate a multifaceted approach among all parties to recognize and mitigate the risks associated with opioid use.
15		**Argoff** Healthcare providers can play a role by following universal precautions, incorporating screening strategies, and

monitoring patient adherence to prescription opioids.

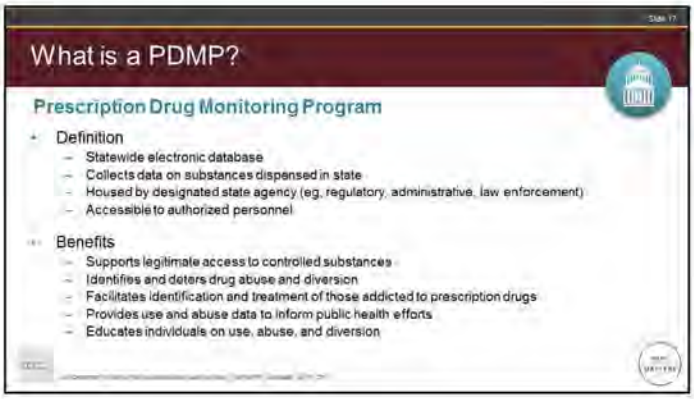
Some of the elements of universal precautions are outlined here, and include establishing a diagnosis, incorporating the use of a treatment agreement, periodic pain assessments, reviewing the diagnosis, and of course, ensuring appropriate documentation.

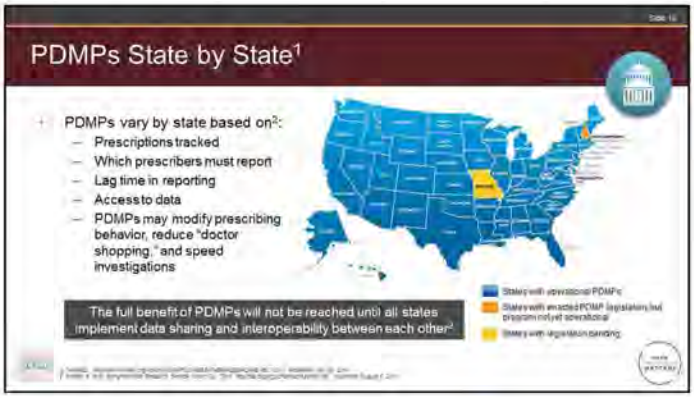
In terms of screening, there are various instruments that we can use as healthcare providers to identify the risk of opioid abuse in our patients, and some of them are listed here.

We also have adherence monitoring approaches. State-specific prescription drug monitoring programs provide us with some insight into the use of opioids by a particular patient, but these may vary widely between states.

Random drug screens are important. Random urine drug screens may be a way of confirming or evaluating adherence for the people to whom we prescribe medications, as is pill counting to see whether it appears that the person who we're prescribing the medication to is actually using it in a way that we have prescribed it and is adhering to that regimen.
Keep in mind, even though we might consider any of our patients to be low risk for opioid abuse, no

		patient has zero risk. As healthcare providers, we are the front line against opioid abuse, and as such, we need to use multiple methods to support safe and effective use of the treatments we prescribe.
16		**Argoff** The patient has responsibilities as well, which we can help through patient education. For example, we can help the patient understand how to safely use, store, and dispose of opioids. From a safe use point of view, we can encourage our patients to take their medications as prescribed, to understand the risks associated with chronic opioid therapy, and to be aware of inappropriate use and its consequences. From a safe storage point of view, we don't want a person's opioid therapy to be accessible to their children or other family members. Just a single dose can be very dangerous to someone who is not supposed to be using an opioid analgesic. So opioids should be locked or hidden to avoid access by family or friends and of course our patients need to know never to share their opioids with others because again, a single dose can be regrettably but realistically catastrophic with respect to adverse outcomes, including death.

		Safe disposal is also very important. There are increasing numbers of community-sponsored take-back programs so opioids in a particular community may be disposed of through this approach and if that's not available, the Office of Drug Control national policy recommendations have been established and can be accessed to allow for an environmentally friendly disposal approach to these medications.
17		**Argoff** So what exactly is a prescription drug monitoring program, or PDMP, for short? By definition it is a statewide electronic database and it is designed to collect data on substances dispensed in that particular state. It is housed within a designated state agency, so it could be a regulatory, administrative or law enforcement agency; this may vary from state to state and it's accessible only by authorized personnel. What are the potential benefits? Well, this is a program that allows us to see what controlled substances a specific patient may be receiving in that state and in that way it helps to support legitimate access to controlled substances. PDMPs may also be able to help identify and deter drug abuse and diversion. They may be able to facilitate identification and treatment of those addicted to

		prescription drugs by detecting certain patterns, which can be very helpful in cases where addiction is not obvious. They also allow you to establish that you will be monitoring every patient's opioid use patterns. They may provide use and abuse data to support public health efforts to help educate all of us, especially our patients, on how to effectively use medications and how we can all play a role in limiting abuse and hopefully reduce diversion.
18		**Argoff** As you see, Missouri is the only state currently without an enacted prescription drug monitoring program and most other states have an operational prescription drug monitoring program. PDMPs vary state by state, but in general they all are constructed to help clinicians understand how patients use prescription opioids, which may then impact our prescribing behavior. This can be used to help reduce doctor shopping and to promote greater transparency. It's also fair to say that the full benefit of prescription drug monitoring programs will not be reached until all states implement data sharing and interoperability between each other to ensure transparency of opioid use across state lines.

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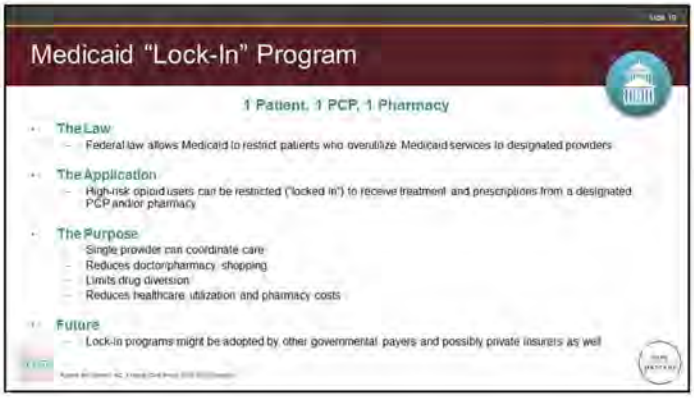
19		**Argoff** Those of you with patients on Medicaid may be aware of its lock-in program, which provides some ideas on how to limit abuse as well. Federal law allows Medicaid to restrict patients who overutilize Medicaid services to designated providers. It does so by requiring a patient to be seen by one HCP and obtain their prescriptions from a single pharmacy. The purpose of this is to empower a single provider to coordinate care, to reduce doctor and pharmacy shopping, to limit drug diversion, and to reduce healthcare utilization and pharmacy cost. In the future, this model may be adopted by other governmental payers beyond Medicaid and even by private insurers as well to accomplish the same goals.
20		**Argoff** As we alluded to earlier, controlled substance scheduling of opioids can also help address prescription opioid abuse. As you know, the lower the number, the higher the potential for abuse and dependence. Hydrocodone products were rescheduled from Schedule 3 to Schedule 2 in late 2014, which makes the process of obtaining a prescription and refills somewhat more difficult.
21		**Argoff**

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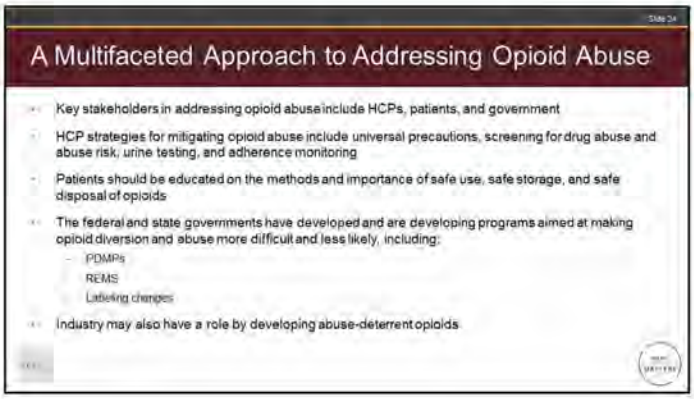
		The US Food and Drug Administration has also established a series of steps designed to help reduce opioid-related risks, and these are known collectively as opioid risk evaluation and mitigation strategies, or REMS. They include the establishment of a medication guide or patient package inserts, a communication plan, one or more elements to assure safe use, an implementation system and a timetable for reporting the REMS assessments to see if these strategies have been effective or not.
22		**Argoff** REMS programs differ by opioid class. For example, immediate-release opioids do not require a risk evaluation and mitigation strategy program per FDA guidelines. The transmucosal immediate-release fentanyl products or TIRFs do involve a REMS program and practitioner and manufacturer participation is mandatory, with access restricted to prescribers who have completed certain educational activities and have scored successfully on an examination. In other words, not everyone with a DEA number can prescribe these medications. There has to be an additional set of educational activity before that can happen. With extended-release and long-

		acting opioid therapy, participation in the REMS program is not mandatory for the practitioner and access is not restricted to prescribers who have fulfilled certain criteria.
23		**Argoff** The federal government, through the FDA, can also change what's in the package insert of a product. Here, you see some changes in the package inserts of extended-release opioids that were implemented in 2013. As you can see, the indication itself for extended-release and long-acting opioids has changed in two ways. The first change specifies that extended release or long-acting opioids are indicated for management of pain severe enough to require daily around the clock, long-term opioid treatment and for which alternative treatments are inadequate. The second change states that these agents should be reserved for use in patients for whom alternative treatment options (for example, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. There are also post-market~~ing~~ studies the FDA now requires. The FDA specifically is requiring new

		studies to further assess the known serious risks of misuse, abuse, and increased sensitivity to pain (sometimes known as hyperalgesia), addiction, overdose, and death. Finally, there is also a new boxed warning that states QUOTE chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome or NOWS. CLOSE QUOTE.
24		**Argoff** To summarize, we need to really consider a multifaceted approach to addressing opioid abuse. The key stakeholders in this multifaceted approach include healthcare providers, patients, government, as well as industry. As we discussed, healthcare provider strategies for mitigating opioid abuse include universal precautions, screening for drug abuse and abuse risk, urine testing, and adherence monitoring. Patients should also be educated, specifically on the methods and importance of safe use, safe storage, and safe disposal of opioids. The Federal and State government have developed and continue to develop programs aimed at making opioid diversion and abuse more difficult and less likely including the use of prescription drug monitoring programs, the

		risk evaluation and mitigation strategy programs or REMS, and labeling changes. I hope you enjoyed this chapter of the program and better understand the role that healthcare providers, patients, and the government play in a multifaceted abuse mitigation strategy. Industry may play a role in helping mitigate opioid abuse. To tell you a little more about this and the potential role of abuse deterrent opioids, please watch the final chapter in this series presented by Dr. Michael Brennan.
	Video Image	**Closing Music**

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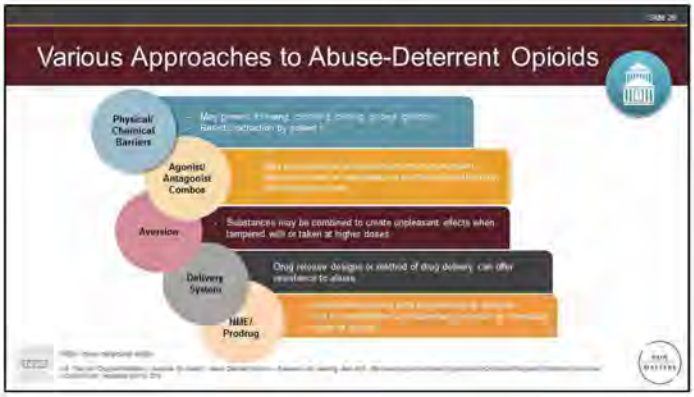
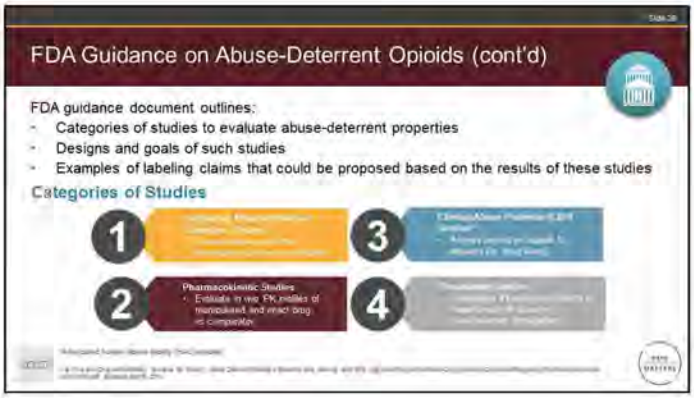
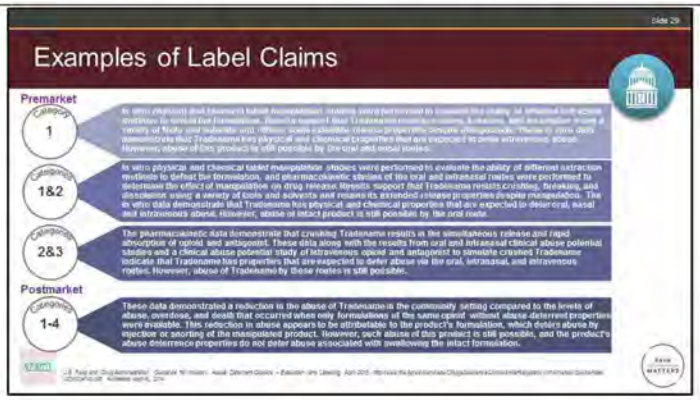
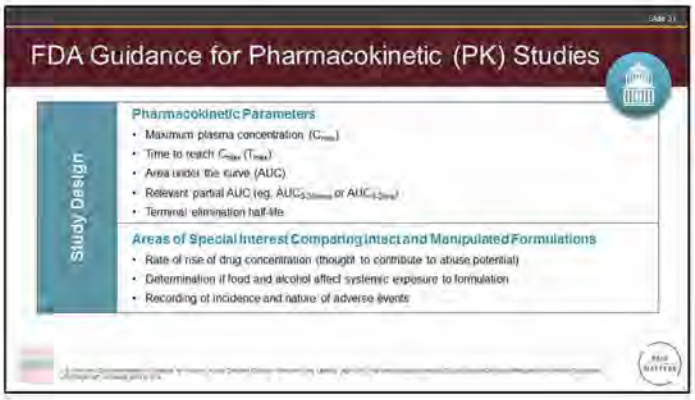
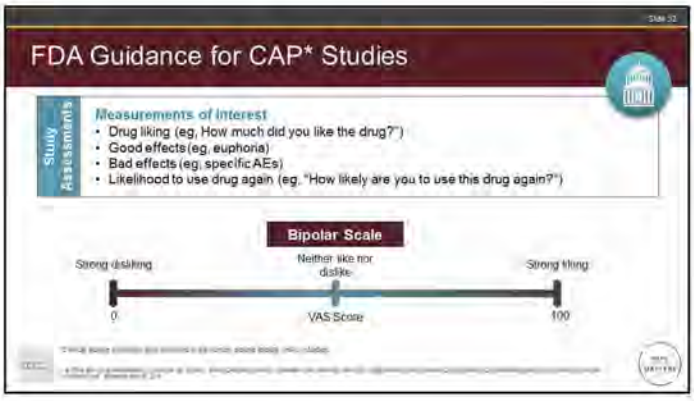
Part 4 – Developing Abuse-Deterrent Opioids		
25		**Brennan** I'm Michael Brennan and I'm the medical director and chief medical officer of the Pain Center of Fairfield in Fairfield, Connecticut. I'm also associate medical director for the Chronic Pain and Recovery Center at the Silver Hill Hospital in New Canaan, Connecticut. Over the previous chapters in this program, you heard about some of the issues associated with opioid use and how healthcare providers, patients, and the government can help reduce risks associated with opioid therapy. Now, I'm gonna to tell you about the potential role that the pharmaceutical industry might play in mitigating opioid abuse, specifically through the development of abuse-deterrent opioids.
26		**Brennan** You'll see that there are ~~5~~ 7 general approaches that have been recognized by the FDA as categories of abuse deterrent opioids. These include physical/chemical barriers, agonist/antagonist combinations, aversion substances added to the analgesic, delivery system characteristics, new molecular entities and ~~and finally,~~ pro-drugs, combination approaches, and novel approaches. Regardless of the different

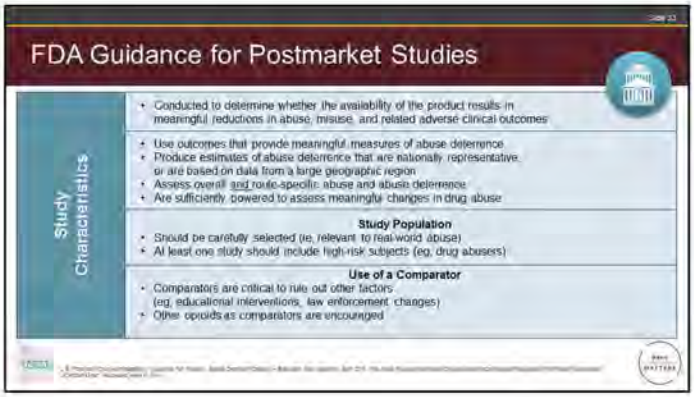
		approaches to these formulations, keep in mind that all of these products share one important commonality: when the medication is taken as directed or intended, the opioid works like a medication that does not include abuse deterrent properties. It's only when the formulation is tampered with that the abuse-deterrent properties become evident. So that's the technical issue, right? Creating a drug that will work for pain, but at the same time making it difficult for somebody to want to abuse that drug or make abusing the drug less beneficial.
27		**Brennan** So where does the industry get their guidance? There was a guiding principle ~~draft~~ document that was published by the FDA in April 201~~3~~5. I'm going to provide you with an overview of what's contained within the ~~draft~~ guidance for developing abuse-deterrent opioid formulations.
28		**Brennan** There are four study categories that can be used to assess the potential abuse-deterrent properties of an opioid. And as we get into the types of abuse deterrent technologies, it'll become clear that certain technologies may meet one type of study and prove beneficial, but not necessarily a different type.

		The first group of studies are laboratory manipulation and extraction studies. These determine if tampering with the drug can override the formulation and provide access to the unadultered opioid. The next are pharmacokinetic studies. These studies look at how the abuse-deterrent properties exert an effect on the pharmacokinetic profile of the drug, and after the drug has been manipulated in the lab, if there's an alteration in the pharmacokinetic profile. Examples of such alterations may include changes in bioavailability of the drug or changes to peak plasma concentration. The third type of test is the clinical abuse potential study. These are studies that look to see how attractive or liked by recreational drug users the drug is in its unaltered and altered states. Finally, and perhaps the greatest hurdle, will be the postmarket~~ing~~ studies. Has there been a demonstrable reduction in abuse based upon the availability of a certain drug in the market? As you can imagine, it's going to take several years to determine if there's been an effect.
29		**Brennan** Now, there are ~~four tiers of~~ different label claims that can be

		achieved and may be proposed for the package insert, and these depend on the results of studies conducted. ~~These label tiers generally correspond to the study categories we just reviewed.~~ ~~The first tier is that the medication has been formulated with a physicochemical barrier to abuse.~~ ~~Another claim is that the drug is expected to reduce or block the effect of the opioid when the product is manipulated.~~ ~~The third is that the medication is expected to result in a meaningful reduction in abuse and finally, the fourth tier that everyone will be trying to achieve, is that the formulation has been shown to reduce abuse in the community.~~
30		**Brennan** Let's look carefully at the manipulation studies that have been outlined by the FDA. The goal of this type of study is to see, through physical or chemical manipulation, if a drug can be easily extracted from the formulation. These studies look at particle size and determine if a small enough particle of active drug can be extracted through various methods (including crushing, grinding, hammering, chemical reactions, and changing temperature). In other words, think of whatever a closet chemist

		might try to do to get that active drug out of the delivery system. Let me emphasize this again. Remember, the molecules we're using are the same 13 or so molecules that are available in the United States that are deemed opioid analgesics. So it's not the molecule itself that's being evaluated. What we're looking at are the formulations carrying those molecules. Can those formulations protect and make it so the drug is more difficult to be used in ways other than intended? And the studies also include, as I mentioned, solubility studies and we're trying to target three specific means of abuse: snorting, smoking, and injecting. Why are these three the types mentioned by the FDA? Because these are the approaches more often linked to substance abuse and addiction.
31		**Brennan** The second type of study that I mentioned earlier are PK studies. So for those of you who can remember back to medical school, pharmacokinetics look at how a drug acts in the system by looking at plasma concentration. So we're interested at looking at maximum plasma concentration, the time to reach this maximum, the total area under the curve, a relevant partial area under the curve, which we think is very important in substance abuse that is, how quickly does the drug get

		absorbed, and what's the terminal elimination half-life? What's very important in these trials is to try and understand if manipulation of the drug has an effect on the rate of rise of drug concentration. We want to determine if other substances, benign substances (food, alcohol, water, other common solutions, such as soda) might affect the way the drug is ultimately absorbed, and also record the incidence of adverse events.
32		**Brennan** Let's take a look at what are known in the draft guidance as CAP, or Clinical Abuse Potential, studies. These are what we used to refer to as the human abuse liability potential of a drug, measured in a way that many clinicians find interesting. This involves exposing recreational non-dependent individuals to the opioid formulation using well-controlled studies. So people who aren't physically dependent on an opioid, but will use them recreationally and have enough experience to understand what the normal high of an opioid would feel like. And what the subjects are asked to do is tell us how much they like the drug. So they're given a visual analog scale, similar to this bipolar scale on the slide, where the individual is asked after being exposed to the drug how much they like it or dislike it.

		And they're asked questions, questions that you and I won't ask in our clinics, like how high are you, what's the euphoria like? I mean, we may ask our patients about adverse events, but here we're trying to tease out different information from these recreational drug abusers and then the all-important question, how likely are you to use this drug if you can get it?
33		**Brennan** The fourth category describes postmarket~~ing~~ studies to be conducted in order to examine if a formulation is likely to decrease abuse in the community. The goals are to try and provide estimates of how the drug is being abused, whether it's being snorted or injected, and has this formulation demonstrated a reduction in abuse. These studies require sufficient numbers to determine whether or not there is a real or an artificial effect, and as such, study populations are going to have to be carefully selected to target real-world abusers. Comparators will also be looked at to see if changes are due to the formulation or other factors, like educational programs or changes in law enforcement. There will also likely be other opioid comparators as part of these studies.

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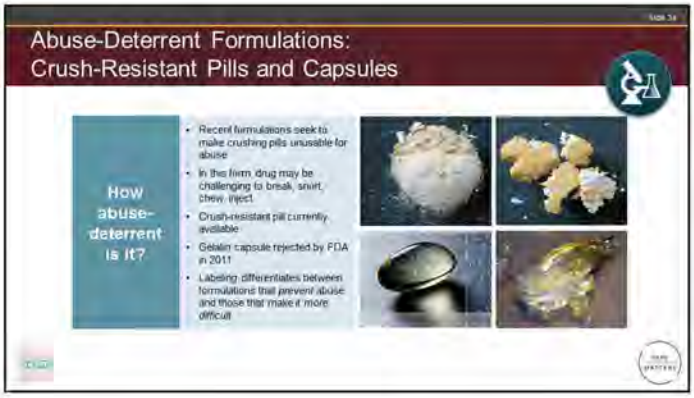
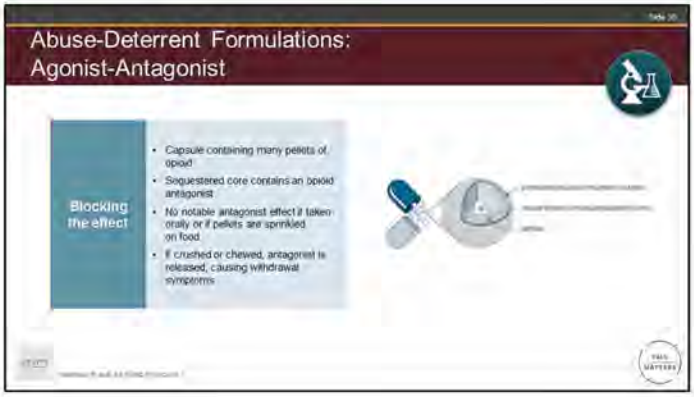
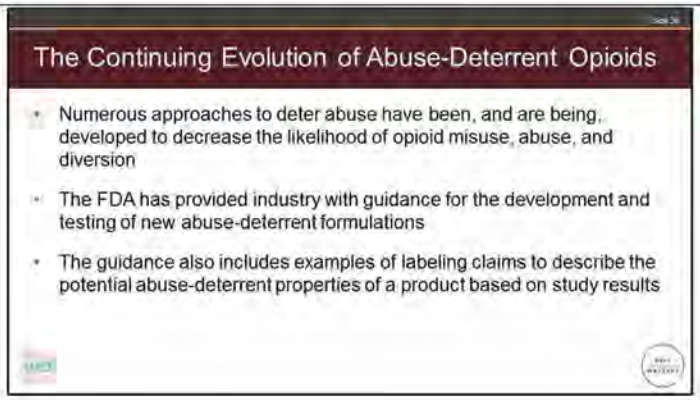
Pain Matters: Evolving Roles, Same Goals Video Script/Storyboard

34		**Brennan** Now that we've reviewed the studies that may be conducted to test an abuse-deterrent opioid formulation, let's switch gears and look at some of the different approaches. Perhaps the most common form of abuse deterrent is the crush-resistant pill and capsules. All of these have in common a process that makes it very difficult to crush the pill, or as we see in the bottom right picture on this slide, a pill that if crushed becomes a viscous or gelatinous substance that's very difficult, if not impossible, to draw up in a syringe or to snort.
35		**Brennan** Here we see a different approach, which is the use of agonist/antagonist combinations. For example, in a medication with a sequestered opioid antagonist core, the antagonist will only be released if the formulation is manipulated. With any of these strategies, we have to remember that no technology can completely prevent abuse. Only time will tell if these technologies are successful in helping to deter abuse.
36		**Brennan** In summary, different approaches to opioid deterrence continue to evolve. This is a very exciting science and a very exciting time to offer our patients drugs that may make the abuse of their drugs

		more difficult. It will take time to work through the testing, especially for postmarket~~ing~~ studies, but as these studies are completed and reviewed by the FDA, abuse-deterrent opioids may be able to include language in their package inserts to let clinicians know what effect the formulation is likely to have on abuse and abuse potential, which will ultimately help us make better informed decisions for our patients. Thank you for watching this chapter on the development of abuse-deterrent opioids. If you haven't already, please be sure to return to the main menu to watch the other chapters, including Jeff Gudin talking about the complexities we face in pain management, and Charles Argoff talking about a Multi-Faceted Approach to Address Prescription Opioid Abuse. On behalf of all 3 faculty and Teva Pharmaceuticals, we hope you enjoyed the program and thank you for your time.
	Video Image	**Closing Music**